International Journal of Research in Medical Sciences
Dhakad V et al. Int J Res Med Sci. 2019 May;7(5):1837-1841
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20191687

Original Research Article

Sequential C-reactive protein: a cheap and a valuable biomarker in patients with sepsis

Vinod Dhakad, Sushma Trikha, Neelima Singh*, Archana Kansal

Department of Medicine, G. R. Medical College, Gwalior, Madhya Pradesh, India

Received: 08 March 2019
Revised: 20 March 2019
Accepted: 04 April 2019

***Correspondence:**
Dr. Neelima Singh,
E-mail: neelimajadon@yahoo.com

ABSTRACT

Background: C-reactive protein (CRP) is a valuable biomarker of sepsis. Levels of CRP increase very rapidly in response to infection, and decrease just as rapidly with the resolution of the condition. The aim of the research was to study, C-reactive protein levels in patients of sepsis and to study the pattern of CRP levels in patients of Sepsis with hypertension, diabetes, smokers and alcoholics.
Methods: This prospective observational cohort study was conducted from December 2016 to September 2018 in 100 cases of sepsis. Patients presenting in emergency with sepsis were included as subjects. C- reactive protein was measured in every patient at the time of admission and after 72 hours. Facts related to history, clinical examination and biochemical parameters were recorded in a pretyped proforma. Data were analyzed using SPSS software.
Results: Males outnumbered females. Most of the patients40(40%) were in the age group of less than 30 years age group. CRP levels were markedly elevated in patients with diabetes mellitus (92.2±102.63) as compared to patients with hypertension (36.66±26.97) or both (24.20±12.87). CRP levels were higher in alcoholics (60.59±44.20) as compared to smokers (13.37±10.96). CRP levels decreased significantly after 72 hours compared to CRP levels at the time of admission ($p < 0.001$) across all patients suggestive of acute infection.
Conclusions: Serial CRP measurement, rather than a single determination at the time of admission, is cheap and valuable in the diagnosis of sepsis and in monitoring the response to therapy. CRP levels shows exaggerated response in diabetes mellitus and alcoholics with sepsis in this study.

Keywords: Biomarker, C-reactive protein, Sepsis

INTRODUCTION

C-reactive protein is a valuable biomarker of sepsis. Levels of CRP increase very rapidly in response to trauma, inflammation and infection, and decrease just as rapidly with the resolution of the condition. Determination of CRP is a cheap, consistent and reproducible test.[1] CRP in combination with systemic inflammatory response syndrome (SIRS) was useful to diagnose infection in Intensive care unit patients.[2]

CRP is produced primarily in hepatocytes. Other sites include smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes. CRP is the only acute phase protein directly involved in the clearance of micro-organisms. There is now growing evidence that CRP has different roles in inflammatory processes and host responses to infection.[3]

Its application in infectious diseases is unquestionable. CRP is secreted by the liver in response to a variety of inflammatory cytokines. In the general population, CRP

values range between 0.1 and 10 mg/L in adults. Measurement of CRP can be used not only to monitor various inflammatory states and many different disorders, but also to assess the severity of tissue damage injury.[4]

Aim and objectives

- To study, C-reactive protein levels in patients of Sepsis.
- To study the pattern of CRP levels in patients of Sepsis with hypertension, diabetes, smokers and alcoholics

METHODS

This was a prospective observational cohort study which was conducted from December 2016 to September 2018 in 100 cases of sepsis. Patients presenting with sepsis and septic shock, were included as subjects. Sepsis was diagnosed on the basis of systemic inflammatory response (SIRS) associated with source of infection. Systemic inflammatory response included four criteria out of which at least two were required to qualify for SIRS. Criteria included, leucocytosis/ leucopenia, hypothermia/ hyperthermia, tachycardia more than 90/minute and tachypnoea more than 22/minute. Maximum age of the patient was 80 years and the youngest patient was 14 years of age. Exclusion criteria: was Acquired immunodeficiency syndrome. The Hospital Ethics Committee approved the study design. The present study analysed the importance of serial CRP with rise and fall over 72 hours in the diagnosis of acute infection.

Data collected were entered in a pretyped proforma which included chief complaints, past medical history, addictions, vital signs for the severity of sepsis, quick Sequential Organ Failure Assessment (qSOFA) score and routine biochemical parameters in addition to CRP measurements. Measurement of CRP was done by immunoturbidimetric method. CRP levels were measured at admission and after 72 hours. Statistical analysis was done using SPSS software.

RESULTS

Out of hundred patients73 (73%) were males and 27(27%) females. Mean CRP level in females was 57.52±58.34 and in males 61.69±65.65. Mean CRP levels decreased to 16.74±16.81 and 22.08±28.81 after 72 hours in females and males respectively. CRP levels decreased significantly after 72 hours compared to CRP level on admission across all patients in this study suggestive of acute infection (p<0.001) (Table 1).

Most of the patients 40 (40%) were in the age group of <30 years with mean CRP levels 75.28±93.97. Mean CRP level was 51.18±29.95, 53.97±22.01 and 23.97±14.43 in the age group 31-50 years, 51-70 and 71-90 years respectively.

Table 1: Correlation of serial CRP levels (mean) in sepsis and gender.

Gender	No. of cases	CRP (on admission)	CRP (after 72 hrs)
F	27	57.52±58.34	16.74±16.81
M	73	61.69±65.65	22.08±28.81

(p<0.001)

Table 2: Correlation of serial CRP levels (mean) in sepsis with different age groups.

Age group	No. of patients	CRP (on admission)	CRP (after 72 hrs)
10 to 30	40	75.28±93.97	27.84±36.53
31 to 50	26	51.18±29.95	15.61±11.13
51 to 70	30	53.97±22.01	17.01±11.37
71 to 90	4	23.97±14.43	7.5±3.86

P=0.001

After 72 hours there was a fall in CRP levels to 27.84±36.53, 15.61±11.13, 17.01±11.37 and 7.5±3.86 in the age group of <30 years, 31-50 years,51-70 and 71-90 years respectively Table 2. Mean CRP level was significantly low after 72 hours as compared to CRP level at the time of admission across all age groups in patients of sepsis. P=0.001 (Table 2). 10 (10%) patients were hypertensives, 7 (7%) were having diabetes mellitus and 2 (2%) patients were both diabetic and hypertensives. Mean CRP levels were 92.2±102.63, 24.20±12.87 and 36.66±26.97 in diabetics, diabetes with hypertension and hypertensives respectively. CRP level was highest among the patients of diabetes (92.2±102.63) as compared to patients with hypertension or both (Table 3). After 72 hours mean CRP levels were 18.37±17.19, 7.8±5.09 and 10.12±3.39 in diabetics, diabetes with hypertension and hypertensives respectively. 81 (81%) cases were neither diabetic nor hypertensives and had CRP levels of 61.65±62.62 at the time of admission and the levels came down to 22.40±27.19 after 72 hours.

Decline in CRP was significant across all patients. P value <0.001 (Table 3).

Table 3: Correlation of serial CRP levels (mean) in sepsis with diabetes and hypertension.

Past history	No. of patients	CRP (on admission)	CRP (after 72 hrs)
DM	7 (7%)	92.2±102.63	18.37±17.19
DM and HTN	2 (2%)	24.20±12.87	7.8±5.09
HTN	10 (10%)	36.66±26.97	10.12±3.39
Nil	810 (81%)	61.65±62.62	22.40±27.19
Total	100		

P value <0.001

Table 4: Correlation of serial CRP levels (mean) in alcoholics and smokers with sepsis.

Personal	No. of cases	CRP (on admission)	CRP (after 72 hrs)
Alcoholic	6	60.59±44.20	17.53±13.30
Smoking	3	13.37±10.96	7.30±2.95
Nil	91	58.37±59.72	20.89±25.70
Total	100		

P value <0.001

Out of 100 patients, 6 (6%) were alcoholic and 3 (3%) were smokers. Mean CRP level in alcoholics was 60.59±44.20 at admission and17.53±13.30 after 72 hours. In smokers mean CRP levels was 13.37±10.96 at the time of admission and 7.30±2.95 after 72 hours. CRP level were higher in alcoholics (60.59±44.20) as compared to smokers (13.37±10.96) (Table 4). 91% patients without addiction had CRP levels 58.37±59.72 at the time of admission and CRP levels 20.89±25.70 after 72 hours. CRP levels decreased significantly after 72 hours compared to CRP level on admission across all cases. (p<0.001) (Table 4).

Table 5: Correlation of serial CRP levels (mean) with blood pressure, pulse and respiratory rate in patients with sepsis.

Vital parameters	No. of cases	CRP (on admission)	CRP (after 72 hrs)
Normal blood pressure	69 (69%)	66.49±73.59	22.64±29.18
Hypertension/ hypotension	31 (31%)	47.40±27.75	17.10±11.83
Normal pulse	60 (60%)	64.49±79.15	23.61±30.50
Tachycardia/ Bradycardia	40 (40%)	54.69±26.42	16.90±13.18
Normal respiratory rate	74 (74%)	66.52±71.51	23.43±27.75
Increased respiratory rate	26 (26%)	59.66±56.64	20.46±25.56

Total 69 (69%) were normotensives and 31(31%) were having either hypotension/hypertension. Mean CRP was 66.49±73.59 and 47.40±27.75 in normotensives and hypertensives/hypotensives respectively at the time of admission and 22.64±29.18 and17.10±11.83 in normotensives and hypertensives/hypotensives after 72 hours respectively (Table 5).

Total 60 (60%) cases presented with normal pulse rate and 40 (40%) cases with either tachycardia or bradycardia. Mean CRP was 64.49±79.15 in 60 (60%) cases with normal pulse rate and a mean CRP of 54.69±26.42 was found to be present in 40 (40%) with tachycardia/ bradycardia. After 72 hours CRP levels were 23.61±30.50 and 16.90±13.18 in cases with normal pulse rate and those with tachycardia/ bradycardia respectively (Table 5).

Total 74 (74%) cases presented with normal respiratory rate and 26 (26%) cases with tachypnoea. Mean CRP was 66.52±71.51in patients with normal respiratory rate and 59.66±56.64 in those with tachypnoea.

After 72 hours CRP levels declined to 23.43±27.75 and 20.46±25.56 in those with normal respiratory rate and tachypnoea respectively (Table 5).

Table 6: Correlation of serial CRP levels (mean) with pallor, oedema and jaundice.

Clinical signs (72 hrs)	No. of cases	CRP (on admission)	CRP (after 72 hrs)
Pallor	19 (19%)	52.82±29.81	17.68±12.75
Oedema	20 (20%)	45.64±22.72	14.98±10.70
Jaundice	9 (9%)	39.49±29.41	12.24±9.24

CRP level was highest in19 (19%) patients with pallor (52.82±29.81) as compared to 20 (20%) patients with oedema (45.64±22.72) and 9 (9%) with jaundice (39.49±29.41). After 72 hours, mean CRP was 17.68±12.75,14.98±10.70 and 12.24±9.24 in patients with pallor, oedema and jaundice respectively (Table 6).

Table 7: Correlation of serial CRP levels (mean) with the symptoms of sepsis.

Complaints	No. of patients	CRP (on admission)	CRP (after72 hrs)
Headache	3	117.35±154.03	49.24±66.06
Convulsion	4	54.95±36.56	20.00±23.62
Breathlessness	23	59.04±67.92	22.33±29.53
Vomiting	21	75.32±93.78	28.91±40.07
Altered sensorium	24	65.83±65.81	14.12±29.47

(p<0.001).

Only 3 (3%) cases had headache with CRP levels 117.35±154.03. 4 (4%) had convulsion with mean CRP 54.95±36.56,23 (23%) had breathlessness with mean CRP 59.04±67.92, 21 (21%) had vomiting with mean CRP 75.32±93.78 and 24 (24%) had altered sensorium with mean CRP 65.83±65.81. After 72 hours mean CRP was 49.24±66.06, 20.00±23.62, 22.33±29.53, 28.91±40.07, 14.12±29.47 in patients with headache, convulsion, breathlessness, vomiting and altered sensorium respectively. CRP levels significantly decreased after 72 hours across all symptoms (p <0.001) (Table 7).

Table 8: Haematological and biochemical parameters in patient of sepsis.

Investigation	Average	Std Dev	Min-Max
TLC	18337.42 cmm	6439.20	2700-35300
Platelet	1.55 /L	0.92	0.09-4.58
Urea	95.81mg/dl	74.52	15-387
Creatinine	2.71 mg/dl	2.76	0.26-13.9
S. Bilirubin	1.82 mg/dl	2.84	0.3-16.1

Mean TLC, platelets, urea, creatinine and serum bilirubin was 18337.42±6439.20, 1.55±0.92, 95.81±74.52, 2.71±2.76, 1.82± 2.84 respectively (Table 8). 4 (4%) had normal total leucocyte count and mean CRP was 58.60±21.02.

Table 9: Correlation of serial CRP levels (mean) in sepsis with leucocytosis.

TLC	No. of patients	CRP (on admission)	CRP (after 72 hrs)
Normal	4	58.60±21.02	22.20±5.31
Leucocytosis/ leucopenia	96	60.65±64.71	20.87±25.68
Total	100		

Leucocytosis /leucopenia was observed in 96 (96%) cases with sepsis with mean CRP levels of 60.65±64.71. After 72 hours mean CRP was 22.20±5.31 and 20.87±25.68 in patients with normal leucocyte count and those with leucocytosis/ leucopenia respectively (Table 9).

Table 10: Correlation of serial CRP levels (mean) in sepsis with thrombocytopenia.

Platelet	No. of patients	CRP (on admission)	CRP (after 72 hrs)
Normal	44	66.97±81.02	23.41±34.66
Thrombocytopenia	56	55.54±4546	18.97±13.88
Total	100		

Total 44 (44%) with sepsis had normal platelets and a mean CRP of 66.97±81.02 at admission and 23.41±34.66 after 72 hours. On the other hand, 56 (56%) cases had thrombocytopenia with a mean CRP of 55.54±45.46 at admission and 18.97±13.88 after 72 hours (Table 10). Total 61 (61%) had qSOFA score 0, 27 (27%) had qSOFA score 1, 11(11%) had qSOFA score 2 and 1 (1%) had qSOFA score 3. Mean CRP level at admission was 63.46±70.17, 51.27±27.60, 72.53±87.33 and 4 in patients with qSOFA score 0,1,2 and 3 respectively. Table-11 Mean CRP after 72 hours was 24.02±30.71 17.48±12.51, 13.58±6.08 and 5.9 in patients with Qsofa 0,1,2 and 3 respectively.

All the patients survived in this study.

DISCUSSION

Serial CRP measurements rather than a single determination are valuable in the diagnosis of sepsis and infection as well as in monitoring the response to therapy. CRP levels were significantly low after 72 hours compared to CRP levels on admission ($p < 0.001$) across all patients suggestive of acute infection or sepsis.

Males 73 (73%) outnumbered females 27 (27%). CRP levels were similar between genders in present study (Table 1). According to Feldman M, CRP levels were identical in women and men, as in our study.[5]

Reports of Kalil et al, found extremes of age (70 years) as the most common risk factor for severe sepsis and septic shock.[6] In present study, the most common age group for sepsis was less than 30 years (Table 1).

CRP level was highest among the patients having diabetes (92.2±102.63) as compared to patients with hypertension (36.66±26.97) or both (24.20±12.87). It appears that the response to sepsis in diabetics is exaggerated compared to hypertension.

In diabetes there is altered immunity that results in chronic inflammation, immune suppression, and significant infection morbidity. Clinical studies indicate a higher susceptibility for diabetic patients to acquire infections.[7] A study by King DE et al, suggest an association between glycemic control and systemic inflammation in people with diabetes mellitus.[8] CRP concentrations increased with increasing HbA1c (Glycosylated hemoglobin) levels.[8] This explains high CRP levels in sepsis with diabetes mellitus.

Another study has established a strong positive association between poor blood sugar control and elevated CRP levels.[9]

The findings of a study by Mattace-Raso et al, support a role of C-reactive protein in the development, of isolated systolic hypertension in apparently healthy older adults.[10]

In yet another study by Hage FG, a role of CRP in the development of endothelial dysfunction, vascular stiffness and elevated blood pressure is evident.[11]

In present study, CRP levels were comparable in normotensives and hypertensives. CRP levels were higher in alcoholics (60.59±44.20) as compared to smokers (13.37±10.96) (Table 4). Alcoholics are prone to severe infections and that the immune system is impaired by chronic ethanol abuse. According to. Vanbiervlietv et al, CRP is an accurate marker of alcoholic hepatitis.[12] Kalil et al, studied risk factors for severe sepsis and septic shock which included extremes of age, alcoholism, diabetes mellitus in addition to other risk factors.[6]

CRP level increases in the presence of acute or chronic inflammation or infections.[13] CRP is both a marker of acute and chronic inflammation in smokers.[14] Data suggest a positive association between smoking status and raised CRP levels emphasizing the preventive message that smoking is not safe. Smoking cessation has a favourable effect on CRP, though this benefit is not evident in the short-term.[15] In present study CRP levels in smokers were comparable with non smokers. Diabetes mellitus and alcoholism appear to be important comorbidities having influence on CRP levels according to our study.

Another important point which was noted was low CRP levels in Qsofa3.Only further studies will explain this point (Table 11).

Table 11: Correlation of serial CRP (mean) with qSOFA score.

qSOFA score	No. of patients	CRP (on admission)	CRP (after 72 hrs)
0	61 (61%)	63.46±70.17	24.02±30.71
1	27 (27%)	51.27±27.60	17.48±12.51
2	11 (11%)	72.53±87.33	13.58±6.08
3	1 (1%)	4	5.9
Total	100		

Limitations of the study include small size of the study. Only further study in large number of subjects will enlighten us further.

CONCLUSION

Serial CRP measurement, rather than a single determination at the time of admission, is a cheap and valuable marker in the diagnosis of sepsis as well as in monitoring the response to therapy. In alcoholics and diabetes mellitus CRP shows exaggerated response to sepsis.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Pradhan S, Ghimire A, Bhattarai B, Khanal B, Pokharel K, Lamsal M et al. The role of C-reactive protein as a diagnostic predictor of sepsis in a multidisciplinary Intensive Care Unit of a tertiary care center in Nepal. Indian J Crit Care Med. 2016;20(7): 417-20.
2. Reny JL, Vuagnat A, Ract C, Benoit MO, Safar M, Fagon JY. Diagnosis and follow-up of infections in intensive care patients: value of C-reactive protein compared with other clinical and biological variables. Crit Care Med. 2002;30(3):529-35.
3. Sproston NR, Ashworth JJ. Role of C-Reactive Protein at Sites of Inflammation and Infection. Front Immunol. 2018;9:754.
4. Lee DG, Lee KS, Shim JJ, Yoon SM, Bae HG. Prognostic Value of the C-reactive Protein Levels in the Head Injury. J Kor Neurotraumatol Soc. 2005;1(1):57-60.
5. Feldman M, Sbong S. Is CRP, like ESR, Age and Gender Dependent? Rheumatology. 2014; (Sunnyvale) 4:134.
6. Kalil A, Bailey KL. Septic shock. Drugs & Diseases, Critical Care, Medscape, updated: January 5, 2018, Available at: https://emedicine.medscape.com/article/168402-overview.
7. Castro SP, Nathan P, Shapiro I. Diabetes and Sepsis: Preclinical Findings and Clinical Relevance. Diabe Care. 2011;34(3):771-8.
8. King DE, Mainous AG, Buchanan TA, Pearson WS. C-Reactive Protein and Glycemic Control in Adults With Diabetes. Diabe Care. 2003; 26(5):1535-9.
9. Anand A, Maragathamani. Correlation of CRP level with glycemic control in diabetic foot patients and its sequelae. Int Surg J. 2017;4(12):4006-9.
10. Mattace-Raso FU, Verwoert GC, Hofman A, Witteman JC. Inflammation and incident-isolated systolic hypertension in older adults: the Rotterdam study. J Hypertens. 2010;28(5):892-5.
11. Hage FG. C-reactive protein and Hypertension. Journal of Human Hypertension. 2014;28:410-5.
12. Vanbiervliet G, Le Breton F, Rosenthal-Allieri MA, Gelsi E, Marine-Barjoan E, Anty R et al. Serum C-reactive protein: a non-invasive marker of alcoholic hepatitis. Scand J Gastroenterol. 2006;41(12):1473-9.
13. Pieri G, Agarwal B, Burroughs AK. C-reactive protein and bacterial infection in cirrhosis. Ann Gastroenterol. 2014;27:113-20.
14. Tonstad S and Cowan JL. C-reactive protein as a predictor of disease in smokers and former smokers: a review. Int J Clin Pract. 2009;63(11):1634-41.
15. Ohsawa M, Okayama A, Nakamura M, Onoda T, Kato K, Itai K et al. CRP levels are elevated in smokers but unrelated to the number of cigarettes and are decreased by long-term smoking cessation in male smokers. Prev Med. 2005 ;41(2):651-6.

Cite this article as: Dhakad V, Trikha S, Singh N, Kansal A. Sequential C-reactive protein: a cheap and a valuable biomarker in patients with sepsis. Int J Res Med Sci 2019;7:1837-41.